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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/691,711 | 10/23/2003 | Rolf Banholzer | 01-1148-2-C2 | 2056 |
| 28501 | 7590 | 09/25/2008 | EXAMINER | |
| MICHAEL P. MORRIS | | | COPPINS, JANET L | |
| BOEHRINGER INGELHEIM USA CORPORATION | | | ART UNIT | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | |
|------------------------------|------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/691,711 | BANHOLZER ET AL. |
| | Examiner | Art Unit |
| | JANET L. COPPINS | 1626 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 23 April 2008.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-4 and 9-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-4 and 9-15 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____. | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

1. Claims 1-4 and 9-15 are currently pending in the instant application.

Response to Amendment

2. In the Amendment and Response of April 23, 2008, Applicants cancelled claims 16-21.

Claim 16 was previously rejected under 35 USC 112, first paragraph, and claims 17-21 were withdrawn from consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. In the Office Action of February 8, 2007, claims 1-4 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation of the crystalline compounds with the specific DSC and IR spectra found in Figures 1 and 2 of the specification, does not reasonably provide enablement for any crystalline monohydrate of tiotropium bromide. In the following Office Action, the Examiner withdrew the rejections, however reapplys said enablement rejections not only to claims 1-4, but to process of preparation claims 9-15 as well.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in previous Office Actions.

In the instant case, the claims are read as a polymorphic form of tiotropium bromide, named monohydrates of "crystalline tiotropium bromide" with no XRD or other physical properties provided. The phrase "crystalline tiotropium bromide monohydrate" is Applicants' own terminology and might include any monohydrate form of triotropium bromide, since physical data that further describes the monohydrate form have been provided.

The nature of the invention

The nature of the invention is any crystalline monohydrate form of tiotropium bromide, and its process of preparation.

The state of the prior art and the predictability or lack thereof in the art

It is the state of the prior art that polymorphism is the existence of different solid forms (modifications) of a compound which have the same chemical composition but different structures and thus different physical and sometimes also chemical properties (Concise Encyclopedia Chemistry, 1993). It is also the state of the art that any polymorph (including compounds that are characterized by the DSC and IR data in Figures 1 and 2 of the specification) might include other forms without the same X-ray diffraction patterns. It is the state of the prior art that under any given pressure and temperature, other than the conversion points, only one modification is stable, the form with the lowest vapor pressure. Often the conversion rate in the solid phases is so slow that even modifications, which are unstable under normal conditions, can be kept for a long time in their metastable state. This conversion rate can depend on the rate of

temperature change or pressure change (Concise Encyclopedia Chemistry 1993). The predictability or lack thereof in the art is that there can be multiple forms of a solid in existence and these polymorphs are created by varying crystallization processes that began with varying starting materials, utilize varying solvents, varying temperatures and varying reaction times.

There is no method that exists to predict the polymorphs of a solid compound with significant certainty (Rouhi, page 32). Preparing a crystalline form of any compound will cause a specific crystalline form, if in the metastable state, to always resort back to the most thermodynamically stable form.

Furthermore, in addition to exhibiting polymorphism, many compounds form crystalline solvates in which the solvent molecule is an integral part of the crystal structure. Just as every polymorph has its one characteristic X-ray diffraction pattern, so does every solvate. (U.S. Pharmacopia #23, page 1843) Also, sometimes the differences in the diffraction patterns of different polymorphs are relatively minor, and must be very carefully evaluated before a definitive conclusion is reached (U.S. Pharmacopia, page 1843).

*The amount of direction or guidance present and
the presence or absence of working examples*

The only direction or guidance present for the instant process is the specific crystalline forms defined by the data found in Figures 1 and 2 of the instant specification. Applicants argued in the Response of August 8, 2007 that the Examiner failed to provide evidence or objective reasoning to support the assertion that the disclosure was not enabling. Applicants contend on page 2 of said Response, "Applicants have taught how to make and use crystalline tiotropium bromide monohydrate. Unless there is evidence to the contrary, applicants'

teaching of making this particular compound enables them to the full scope of this claim.” The Examiner agrees that Applicants have taught how to make and use the **specific form of crystalline tiotropium monohydrate** discussed in the specification and described in Figures 1 and 2, but has not provided evidence that they are enabled for each and every possible monohydrate crystalline form of tiotropium monohydrate.

The breadth of the claims

The breadth of the claims is any unspecified monohydrate (with any XRD) of tiotropium bromide, and its process of preparation.

The quantity of experimentation needed and

the level of the skill in the art

The quantity of experimentation is extremely high. One would need to prepare crystalline hydrates of tiotropium bromide by many different methods to obtain multiple polymorphic forms, while the specification only provides methods and direction to the process of the preparation of the specific crystalline forms with the DSC and IR spectra found in Figures 1 and 2 of the instant specification. The level of skill in the polymorph art is high. However, without a showing or guidance as to how to make the specific monohydrate form claimed, besides the crystalline forms as described in the specification, it would require undue experimentation to make each and every unspecified polymorph “crystalline tiotropium bromide monohydrate” as recited in claims 1-4 and 9-15. To overcome the rejection, the Examiner recommends inserting physical properties for Applicants’ intended “monohydrate” form into claims 1-4 (i.e. X-RDP, DSC, or IR data enabled in the disclosure), so as to distinguish it from other crystalline monohydrate forms, i.e. she suggests using the same language as recited in

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parent U.S. patents 6,908,928 and 6,777,423 for reciting said crystalline monohydrate form, and that claims 9-15 should be dependent on claims 1-4.

Conclusion

5. In conclusion, claims 1-4 and 9-15 are pending, and all claims currently stand rejected.

Since the pending claims have had the same rejection applied previously, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JANET L. COPPINS whose telephone number is (571)272-0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO /
Primary Examiner, Art Unit 1626

Janet L. Coppins
August 29, 2008